

### REMARKS

Upon entry of the present amendment, claims 69-74, 76-79, 124-127, 129, 130, 137-148, 150-168 170-172, 186, and 190 will be pending. Claims 69, 79, 124-127, 129, 130, 137, 156, 172, 186, and 190 have been amended. Claims 75, 80, 136, 149, 169 and 173 have been cancelled. Support for amended claims can be found throughout the specification as filed, e.g., at page 19 in Table 1. Applicants submit that no new matter has been added.

### Interview Summary

The Applicant's undersigned representative thanks the Examiner for a courteous telephonic interview conducted on August 22, 2006. The Examiner telephoned the representative to clarify that due to an error, the application has not been placed on the Board of Patent Appeals and Interferences docket. The Examiner stated that instead of correcting the error, the finality of the Final Office Action will be withdrawn, and a Non-Final Office Action will be mailed.

### Information Disclosure Statement

Applicants submit herewith an Information Disclosure Statement listing references cited in the application family. Consideration of all references is respectfully requested.

### Priority

According to the Examiner, "the effective date of claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 is deemed the filing date of the instant application, namely July 20, 1999" because these claims "are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure" (at pages 2-3). In view of the arguments and claim amendments below, Applicants submit that these claims are entitled to the earliest priority date of May 6, 1996. Acknowledgement of the earliest priority date is respectfully requested.

### Specification Objections

The Examiner objected to the specification because:

[a]t page 1, paragraph 1, of the specification there is a statement that this application is a division of Application Serial No. 08/836,682. The prior filed application has since issued as U.S. Patent No. 6,107,090; yet the specification does not properly indicate the status of this application (at page 3).

Applicants amended the specification accordingly and request withdrawal of the objections to the specification.

### Claim Objections

The Examiner objected to claims 79, 80, 172, and 173 as allegedly “being of improper dependent form for failing to further limit the subject matter of a previous claim” (at page 3).

According to the Examiner:

insofar as claim 79 is drawn to the method of claim 78, wherein the antibody is a J415 monoclonal antibody, it fails to properly limit the subject matter of the preceding claims because, although the limitations recited in claim 69 require the antibody to compete for binding to PSMA with any a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody, the specification describes the J415 monoclonal antibody as incapable of competing with an E99, a J533, or a J591 monoclonal antibody (at page 4).

Applicants traverse the Examiner's interpretation of claim 79. Claim 79 recites that the antibody of claim 78 is the J591, J533, E99 or the J415 antibody (by referring to the deposited hybridomas). As claim 69, from which claim 78 depends, recites that the claimed antibody can be one which competes for binding with J415, it is clear that the J415 antibody itself has this property, and thus, further narrows the scope of the limitation an antibody that competes for binding with J415. Thus, claim 79 properly depends from claim 78.

Moreover, the Examiner stated that:

[c]laim 172 fails to properly limit the subject matter of claim 126 for the reason claim 79 fails to properly further limit the subject matter of claim 78, which is provided in the paragraph above; and claim 173 fails to properly further limit the subject matter of claim 126 for the reason claim 80 fails to properly further limit the subject matter of claim 78 (at page 5).

For the reasons discussed in connection with claim 79, claim 172 is a proper dependent claims. Claims 80 and 173 have been cancelled. Withdrawal of all objections to claims 79, 80, 172, and 173 is respectfully requested.

The Examiner objected to claim 136 because it allegedly recites "wherein the antibody is a monoclonal antibody or the antigen binding portion thereof is derived from a monoclonal antibody" (at page 5). Applicants cancelled claim 136, obviating the objection. Withdrawal of the objections to claim 136 is respectfully requested.

#### Rejections under 35 U.S.C. § 112, Second Paragraph

##### Indefiniteness

The Examiner rejected claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 as allegedly indefinite (at page 5). According to the Examiner, these claims:

are indefinite because of the recitation in claim 69, for example, of "a monoclonal antibody selected from the group consisting of *an* E99, *a* J425, *a* J533, and *a* J591 monoclonal antibody. . . . Use of such laboratory designations as the sole means of identifying the antibodies to which the claims are directed renders the claims indefinite because different laboratories may use the same designations to define completely distinct hybridomas and/or antibodies produced by hybridomas. . . . Accordingly, it is suggested that the claims be amended to include the depository accession numbers of the hybridomas producing the antibodies to which the claims are directed . . . . (at page 6, emphases in the Action).

Without conceding to the substance of the rejection, Applicants amended claims 69, 79, 124-127, 129, 130, 172, and 186 to recite monoclonal antibodies produced by hybridomas with corresponding accession numbers.

Further, according to the Examiner, these claims are indefinite:

because of the recitation in claim 69, for example, of “which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody” selected from the specified group of monoclonal antibodies. (at page 7)

The Examiner discussed an art-known word “competes” in detail at pages 7-9, and concluded that:

the claims are *not* unambiguously interpreted, as it cannot be determined whether the antibody to which the claims are directed is an antibody that merely inhibits, but does not abrogate the interaction between the selected antibody and PSMA. Moreover, if the claimed antibody merely inhibits binding of the selected antibody to PSMA, it cannot be determined to what requisite extent the claimed antibody must “compete” for binding to PSMA with the selected antibody (at page 9; emphasis in original).

First, Applicants submit that amended claims 69, 79, 124-127, 129, 130, 172, and 186, which now recite monoclonal antibodies produced by hybridomas with corresponding accession numbers. Thus the antibodies are defined with enough precision to allow determination of their competition for binding.

Second, Applicants respectfully disagree with the Office's characterization of George *et al.* (Circulation. 1998; 97:900-906) (“George”), cited in support of the Office's arguments. According to the Examiner at page 9,

George *et al.* illustrates the capricious and arbitrary nature of determinations that different antibodies bind the same or different epitopes, which are based upon the results of competitive binding assays, such as the assays exemplified in the specification. Although each of the described antibodies “competed” to a measurable extent with the other antibodies for binding to the antigen, George *et al.* nevertheless concludes “no competition was achieved”, and the antibodies bind distinct, non-overlapping epitopes.

Applicants respectfully disagree with this assertion. First, this assertion misses the point of the competition limitation, which merely defines a group of antibodies within the invention, namely those antibodies that compete. Furthermore, competition binding assays were used routinely in the art at the time of filing and a determination of whether an antibody competes for binding with another antibody could be objectively and clearly made by one of ordinary skill in

the art at the time of filing. Competition binding assays compare the ability of a first antibody to interfere with binding of a second antibody to its antigen. Such assays can be taken to saturating conditions, and antibodies that do not interfere with binding of the second antibody to its antigen within a reasonable margin of error are considered non-competing antibodies, while those that do displace the second antibody completely or almost completely are considered competing antibodies. This was an accepted and well-understood practice at the time the present application was filed.

Contrary to the assertions made in the Office Action, George further demonstrates this point. Based upon results that showed that an antibody did not interfere with binding of the second antibody to its antigen within a reasonable margin of error, George concludes that the antibodies do not compete for binding. While the Office Action alleges that this is arbitrary, George provides no indication that this determination was subjective. In fact, George makes no attempt to rationalize the determination that the antibodies do not compete for binding (at page 903, paragraph bridging the first and second columns). That is because the results speak for themselves and would be clear to a skilled artisan reviewing that reference.

The Office also stated that “[a]lthough each of the described antibodies ‘competed’ to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes that ‘no competition was achieved’” (at page 9, within quote above). Applicants are at a loss as to why the Office disputes the conclusions of George and contends that George’s antibodies do compete with one another. George carried out scientific experiments and determined that a reasonable threshold for competition, e.g., 5-9% inhibition, indicated no competition (page 903 first and second cols.). As discussed above, George does not rationalize the choice of the threshold, because the results are clear to a skilled practitioner.

The Office also made the following assertions:

[I]t is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any antibody might be deemed capable of “competing” for binding to an antigen with

any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes (at pages 8-9, emphasis in original).

Applicants respectfully disagree. Skilled practitioners routinely carry out planned and controlled experiments to determine whether antibodies compete with one another. They would not arbitrarily add a concentration of an antibody so high as to give false positive results (which seem to be described in the quote above) without testing other concentrations. In fact, the George reference cited by the Examiner, exemplifies standard competition experiments. According to George, "each of the nonbiotinylated mAbs (or control IgM) was used as competitors for binding in different concentrations (0 to 100 $\mu$ g/mL) to the single biotinylated mAb (at concentration giving 50% maximal binding) in the anti- $\alpha$ 2GPI ELISA" (at page 901, second col.). Percentage of inhibition was calculated according to a standard equation (Id.). Thus, George's experiments were carried out with a standard concentration of one antibody and varying concentrations of other antibodies tested for competition. The variables and the controls were planned out according to accepted scientific procedures. Applicants submit that, like George, skilled practitioners would appreciate how to carry out competition assays without obtaining false positives and thus understand the claimed features.

A determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing. In addition, interpretation of such assays to determine whether antibody competes or does not compete for binding was a well-established practice. George exemplifies this by making an affirmative decision that an antibody does or does not compete based upon that fact that a first antibody did not interfere within a reasonable margin of error for the binding of a second antibody to its antigen. A skilled artisan could easily make such a determination and thus clearly know the metes and bounds of the present claims.

The Examiner also noted on page 10 that "the claims are not necessarily limited to the antibodies produced by any of the deposited hybridomas." As discussed above, claims 69, 79, 124-127, 129, 130, 172, and 186 have been amended to recite monoclonal antibodies produced by corresponding hybridomas.

### Written Description

The Examiner rejected claims 75, 149, and 169 as allegedly failing to comply with the written description requirement (at page 10). According to the Examiner at page 11, this is a “new matter” rejection. Claims 75 and 169 recite methods of administering the antibody or antigen binding portion thereof rectally, and the Office propounds that “none of originally filed claims or any of the particular disclosures to which Applicant has referred appears to describe administering an antibody or antigen binding portion thereof *rectally*” (at page 11, emphasis in the Action). Applicants note that at page 15, lines 20-24, the specification states that the present methods can be used to detect disease recurrence “by administering a short range radiolabeled antibody to the mammal and then detecting the label rectally, such as with a transrectal detector probe.” A fair reading of the passage suggests that both the administering and the detecting can be done rectally, supporting the features of claims 75 and 169, and obviating the present rejection.

However, in the interest of expediting prosecution, claims 75 and 169 have been canceled.

Claim 149 recites a method wherein the compound emitting radiation is a beta- and gamma-emitter. The Office rejected claim 149 because “none of originally filed claims or any of the particular disclosures to which Applicant has referred appears to describe administering an antibody or antigen binding portion thereof comprising a cytotoxic drug that is a beta *and* gamma-radiation emitting compound” (at page 12, emphasis in the Action).

Applicants respectfully traverse this rejection. Applicants have clearly described a sufficient number of radioisotopes that administer both beta and gamma radiation in the present application that a skilled artisan would have recognized that Applicants were in possession of this embodiment. To expedite prosecution, Applicants have cancelled claim 149. However, Applicants note that claims directed to antibodies conjugated to a beta emitter would also necessarily include compounds that are a beta emitter and a gamma emitter. The same is also

true for claims directed to a gamma emitter in that a radioisotope that is a gamma and a beta emitter includes a gamma emitter and thus would be covered by the claim.

For at least the reasons presented above, Applicants respectfully request that all written description rejections be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 as allegedly lacking enablement (at page 14). According to the Office,

the specification, **while being enabling for using** a method for treating prostate cancer in a subject, said method comprising administering to the subject an antibody or an antigen binding portion thereof that binds prostate specific membrane antigen (PSMA), wherein said antibody or antigen binding portion thereof is conjugated to a therapeutically effective cytotoxic agent, and wherein said first antibody or antigen binding portion thereof binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, or **while being enabling for using** any other method for treating prostate cancer in a subject, *as taught by the prior art*, which falls within the scope of the present claims, **does not reasonably provide enablement for using** a method for treating prostate cancer in a subject, said method comprising administering to the subject any antibody or antigen binding portion thereof that competes for binding to PSMA with a J591, a J533, a E99, or a J415 monoclonal antibody (at page 14; emphases in original).

As discussed above, Applicants amended claims 69, 79, 124-127, 129, 130, 172, and 186 to recite monoclonal antibodies produced by hybridomas with corresponding accession numbers. Claims 69 and 124-127 have also been amended to recite providing an antibody or antigen binding portion thereof which binds to prostate specific membrane antigen and competes for binding to prostate specific membrane antigen with specific monoclonal antibodies. Applicants submit that these amendments obviate most of the substance of the present enablement rejection. The feature of conjugation of the antibody or the antigen binding portion thereof is discussed below.

The Examiner stated that “the referrals to deposits in the specification at, for example, page 30, lines 15-27, are insufficient assurance that all required deposits have been made and all the conditions of MPEP 608.01(p)(c) are met” (at page 18). Applicants submit herewith a Declaration of Availability, confirming the deposits.

According to the Examiner at page 21,

the specification fails to remedy the deficiency of the prior art to enable the skilled artisan to practice the claimed invention without undue and/or unreasonable experimentation, as it does not particularly describe any one antibody or antigen binding portion thereof that competes for binding to PSMA with an E99, a J415, a J533, and a J591 monoclonal antibody that is not conjugated to a therapeutically effective cytotoxic drug, and does not mediate either ADCC or CMCC, which is used to practice the claimed invention (emphasis added).

Applicants traverse. The Office relied on several references to suggest that naked antibodies may not be therapeutically effective. The references specific to anti-PSMA antibodies are Morris *et al.* (*Clin. Cancer Res.* 2005 Oct 15: 11(2):7454-7461) (“Morris”), Henry *et al.* (*Cancer Res.* 2004 Nov. 1:64:7995-8001) (“Henry”) and McDevitt *et al.* (*Cancer Res.* 2000 Nov 1: 60:6095-6100) (“McDevitt”). Applicants submit that the Office Action misinterpreted the data presented and the relevance of the data presented in these references. As discussed below, the data presented in Morris actually provides evidence that unconjugated anti-PSMA antibodies have therapeutic effect and Henry and McDevitt are not relevant to this analysis.

Morris discusses a pilot trial with an unlabeled anti-PSMA antibody to explore the effects of dose escalating on pharmacokinetics, biodistribution, and ADCC activation in patients having progressive metastatic prostate cancer despite androgen deprivation (see, e.g., page 7459, first sentence of *Discussion*). The antibody used in this trial is a version of J591, which, as described in the present application, competes for binding with monoclonal antibodies J533 and E99.

It appears that at page 22 the Examiner is alleging that only one of fourteen patients had measurable objective response, and thus unconjugated versions of the antibodies recited in the claims would not effectively treat prostate cancer. Applicants submit that this is an inaccurate reflection of what is reported by Morris. Instead, Morris demonstrates that an unconjugated anti-

PSMA antibody does provide therapeutic effect even in a patient population having a very advanced and aggressive form of prostate cancer. Specifically, Morris reports that a patient having histologically documented metastatic prostate cancer that was progressing following castration demonstrated a greater than 50% decline in PSA levels after treatment with a naked version of the J591 antibody (at page 7459, first col.). In addition, three of the patients showed PSA stabilization while participating in the study, and one of those three demonstrated stable disease after the study had completed (*Id.*). The Examiner is reminded that this study was a pilot clinical trial and thus, performed with unoptimized doses administered to a patient population having a very poor prognosis, yet still showed positive results in a number of human patients. Generally, reversal or stabilization of the condition over several months in even a few patients is considered a success for this patient population. Thus, Applicants submit that the results provided in Morris provide evidence of successful treatment of prostate cancer with a naked anti-PSMA antibody, one which competes for binding with monoclonal antibodies J533 and E99.

Furthermore, Morris demonstrates antibody dependent cellular cytotoxicity (ADCC), a mechanism by which naked antibodies are known to exert therapeutic effect, occurs in patients receiving the naked anti-PSMA antibody. Specifically, Morris reports that patients demonstrated ADCC, especially patients receiving the anti-PSMA antibody at increased doses. For example, at page 7459, second column, Morris reports that

dose and ADCC activity were positively correlated, as reflected by the proportion of patients with significant LNCaP lysis, the median percent LNCaP lysis, and the duration of these effects. The highest dose administered was 100 mg, which was tolerated well, and which induced ADCC activation in >80% of patients at 2 hours. Fifty percent of the patients continued to show ADCC activation at 3 weeks. . . . Indeed, even greater and more durable ADCC effects might be seen with higher doses, but these were not tested in this study. (emphasis added)

The Examiner is again reminded that Morris is a pilot trial. This is a very early stage of testing, where optimal dosing regimens have not been developed. Even at this very preliminary stage of testing, on a patient population having a very aggressive form of prostate cancer that has been refractory to all standard treatments, Morris reports stabilization of one patient and positive

clinical response in another using a naked anti-PSMA antibody and further reports that one of the mechanisms by which a naked antibody has therapeutic effect, namely ADCC, is occurring.

The points provided above are further reiterated in Morris. Specifically, at page 7460, second column, Morris states:

In terms of anti-tumor effects, only one patient engaged in a sustained PSA decline of 90% in association with ADCC activation at all dose levels. It is quite possible that this is not the optimal patient population in which to study antitumor effects of an unlabeled antibody. Preclinically, antibodies have been shown to be more effective at protection from progressive disease in the minimal disease setting than at treating established advanced disease (20-23). Patients with a rising PSA after prostatectomy or radiation, but who do not have established metastasis, may be a more suitable population for showing antitumor effects than the patient population tested in this study. It is also possible that doses of antibody in excess of 100 mg might be necessary to induce ADCC activation to sufficient levels to produce significant antitumor effects. (emphases added)

As pointed out by Morris, these studies have not been further pursued. However, the decision not to pursue further human studies with unlabeled antibody was based on drug production (availability) and the possibility that conjugated antibodies may be the "more fruitful" course of action, particularly in these treatment-refractory patients where drug approval studies begin (at page 7460, second col.). Thus, the teachings of Morris suggest that, based on preliminary data, unlabeled antibodies could be used to treat prostate cancer. Financial considerations may prevent that from being a reality, but that is hardly a consideration for patentability or whether the claimed antibodies would have therapeutic effect.

For the reasons discussed above, Applicants submit that the evidence provided by Morris supports the proposition that unconjugated anti-PSMA antibodies, and specifically ones that compete for binding with at least some of the antibodies recited in the claims, can be used to treat and prevent prostate cancer. Thus, the antibodies recited in the claims do function as provided in the present application to provide therapeutic effect.

The remaining references cited by the Examiner do not undermine the evidence provided by Morris.

The Office Action stated that:

Henry et al. (*Cancer Res.* 2004 Nov. 1:64:7995-8001) teaches an anti-PSMA immunoconjugate comprising the drug maytansinoid 1 (DM1) is effective to suppress the growth of prostate cancer in a subject, whereas the unconjugated antibody had no effect upon the growth of cancer cells . . . . In fact, Henry et al. reports the effect of the *naked* antibody upon the growth of the tumor cells in the subject was not significantly different from the effect of the vehicle control . . . . (at page 21, emphasis in original).

Applicants disagree with this characterization. Henry studied dose and schedule regimens of a maytansinoid conjugated anti-PSMA antibody (MLN2704, which is deJ591 conjugated with a maytansinoid) in a xenograft mouse model (see, e.g., Abstract and page 7995, second col.). To demonstrate dose and schedule efficacy with MLN2704, Henry compared the results with those obtained at the same dose and schedule regimen with maytansinoid alone or the antibody administered alone. Henry reports that MLN2704 has a more potent anti-tumor effect than either constituent alone (Abstract).

While the Office Action alleges that this suggests that naked antibody would “have no antitumor activity”, this is simply not the case. Henry specifically acknowledges on page 7999 that “the antibody moiety may engage immune responses that would contribute to efficacy in patients, which cannot be measured in the immunocompromised mouse models studied here.” Thus, the results discussed in Henry do not indicate one way or another whether the naked antibody would be effective. The immunocompromised mouse system simply does not supply the immune molecules and/or cells which would add to the effectiveness of a naked antibody. Moreover, even if the study reported by Henry could measure the efficacy of the naked deJ591 antibody (which it cannot), a difference in effect between a toxin conjugated antibody and a naked antibody given at the same dose, does not suggest, as alleged in the Office Action, that the naked antibody does not have therapeutic effect. It merely demonstrates that the toxin is contributing to the therapeutic effect at the dose tested.

The Office Action also relies on McDevitt *et al.* (*Cancer Res.* 2000 Nov 1: 60:6095-6100) (“McDevitt”) to support the assertion that “the unlabeled monoclonal antibody produced no substantial effect” (at page 22). Again, this is a mischaracterization of the teaching of

McDevitt. McDevitt, like Henry discussed *supra*, used an immunocompromised mouse model (athymic nude mouse model, see, e.g., Abstract). Since immune response to an antibody cannot be measured in this model, this study is not an appropriate indicator of whether a naked anti-PSMA antibody would be therapeutically effective.

The Office Action also cites Stancovski *et al.* (*PNAS USA* .1991; 88:8691-8695), Xu *et al.* (*Int. J. Cancer*. 1993; 53:401-408), Jiang *et al.* (*J. Biol. Chem.* 2005; 280(6):4656-4662), De Santes *et al.* (*Cancer Res.* 1992; 52:1916-1923) to argue that naked antibodies may not have therapeutic effect (at page 24). As discussed above, Morris provides evidence that unconjugated versions of the claimed antibodies could be used to treat prostate cancer. Stancovski, Xu, Jiang, and De Santes all discuss antibodies that bind to completely different antigens than the claimed antibodies for completely different indications. None of these references even mentions PSMA or prostate cancer or provides any reason to discredit that results provided by Morris. As such, none of the Stancovski, Xu, Jiang, and De Santes references are relevant to whether the claimed antibodies are enabled.

The Office Action further cited several references for the proposition that “the mere generalized description of antibodies, as binding a well-characterized tumor-associated antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to adequately describe the antibodies to which the claims are directed, namely antibodies that have an inhibitory and therapeutic effect” (at pages 23-24). These references include Boyer *et al.* (*Int. J. Cancer*. 1999. 82:525-31), Press *et al.* (*J. Immunol.* 1988. 141:4410-17), Riemer *et al.* (*Mol. Immunol.* 2005. 42:1121-24), Pettersen *et al.* (*J. Immunol.* 1999. 162:7031-40), and Bernard *et al.* (*Human Immunol.* 1986. 17:388-405). The references cited for this proposition discuss completely different antigens involved with completely different indications. For example, a large number of the references cited in the Office Action discuss Her2, and antigen directly associated with progression of breast cancer. In the context of this antigen, antagonistic or agonist function of antibodies have been considered for developing a therapeutic. In contrast, as provided throughout the present application, the antibodies recited in the claims can result in cell lysis through immune effector function such as ADCC or complement dependent cytotoxicity

(CDC) or through internalization of conjugates such as radioisotopes or cytotoxins. Therefore, these references provide no indication that the claimed antibodies would not have therapeutic effect via, e.g., immune effector function or internalization of a conjugate.

Moreover, even in the context of other antigens, it is clear that the majority of the references cited by the Office are searching for an antibody with optimal therapeutic effect. For example, the Kim *et al.* reference cited at page 23 of the Office Action (*Int. J. Cancer*. 2002. 102:428-34), discusses several antibodies that bind HER2 and states that “we expect the HRT IgG2a and IgG2b and the HRO IgG2a and IgG2b may exert more antitumor activities on *in vivo* tumor growth” (at page 432, first col., emphasis added). Just because one antibody works better than others for therapeutic effect does not suggest that others do not have potential therapeutic effect-the effect is just not as good. While these types of considerations are important for choosing a drug product, optimal therapeutic effect is not the standard for patentability.

The present claims are directed to antibodies that compete for binding with four specific monoclonal antibodies, J591, J415, J533 and J415, produced by hybridomas with specific ATCC numbers. Thus, the claims recite regions of the PSMA extracellular domain that the antibodies must bind, namely those regions of PSMA that allow the antibody to compete for binding. The majority of the references cited in the Office Action have no information regarding the PSMA antigen or antibodies directed to the specific regions of the PSMA antigen bound by the antibodies and antibody fragments currently claimed. These references provide no evidence that the claimed antibodies would not bind PSMA and have therapeutic effect.

Each of the J591, J415, J533 and E99 antibodies have been shown to bind viable prostate cancer cells. See, e.g., Chang *et al.* (*Cancer Research*. 1999; 59:3192-3198) (“Chang”) submitted herewith as Exhibit A, which discusses binding of monoclonal antibodies J591 and J415 (Abstract). Morris discussed *supra* demonstrates that a version of J591, an antibody disclosed to compete for binding with J533 and E99, results in ADCC in human patients. Based upon the evidence provided in Morris, the knowledge in the art at the time of filing and the guidance provided in the present application, a skilled artisan could make and use an

unconjugated anti-PSMA antibody as a therapeutic. None of the references cited in the Office Action suggest the contrary.

The Office Action essentially reiterated the arguments presented under the Indefiniteness rejections regarding the determination of whether “the antibody ‘competes’ for binding to PSMA with any one of the recited monoclonal antibodies” and concludes that the specification “would not permit the skilled artisan to immediately identify antibodies that are suitable, and would not therefore reasonably enable the practice of the claimed invention without undue and/or unreasonable experimentation” (at page 27). The Office again cites George for its arguments (at pages 28-29).

As discussed *supra*, in the “Indefiniteness” section, Applicants submit that a determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing. In addition, interpretation of such assays to determine whether antibody competes or does not compete for binding was a well-established practice. George exemplifies this by making an affirmative decision that an antibody does or does not compete based upon that fact that a first antibody did not interfere within a reasonable margin of error for the binding of a second antibody to its antigen. A skilled artisan could easily make such a determination without undue experimentation.

The Examiner also stated that “the claims are not necessarily limited to the antibodies produced by any of the deposited hybridomas” (at page 29). As discussed above, the claims have been amended accordingly.

According to the Examiner:

[w]ith particular regard to claim 156, which is directed to the method of claim 69, 125, 126, or 127, wherein the antibody or antigen binding portion thereof is effective to initiate an endogenous host immune function, most murine monoclonal antibodies, which are administered to humans, are effective to initiate an immune response against the antibodies. However, this property of the murine antibodies is generally recognized as a limitation to the effective treatment of

humans, as the resultant immune response preclude repeated administrations that will likely cause undesired and potentially harmful side-effects (e.g., immune hypersensitivity, and perhaps anaphylactic shock). Accordingly, it is submitted that the disclosure does not reasonably enable the use of the claimed invention, as it would not be practiced effectively using antibodies capable of initiating any and all types of endogenous host immune functions, but perhaps only such immune responses that are therapeutically efficacious against prostate cancer cells, such as ADCC or CMCC (at pages 30-31).

Without conceding to the substance of the rejection, Applicants amended claim 156 to recite a method "wherein the antibody or antigen binding portion thereof is effective to initiate an endogenous host immune function that is therapeutically effective against prostate cancer." Withdrawal of the enablement rejection of claim 156 is respectfully requested.

The Examiner asserted at page 31 that claim 190 is not enabled because:

[i]f the antibody or antigen binding portion thereof were administered to a subject prior to the onset of the disease, so as to prevent its occurrence, it is submitted the specification fails to provide the guidance and direction necessary to select patients in whom the intervention is used effectively, and moreover, as PSMA is expressed by normal prostatic epithelial cells, as well as of other normal tissue, it would seem likely that the cost of such treatment would outweigh the benefit, as the treatment would undesirably affect the growth and/or survival of normal cells. Furthermore, there is no factual evidence of record that supports the assertion that the disease is preventable, regardless of whether or not the patient is treated using the claimed invention. Similarly, there is no factual evidence of record that supports the assertion that the claimed method is effective to prevent the progression of the disease, as Morris et al. (cited *supra*), for example, teaches to the contrary monoclonal antibody J591 was not effective to prevent disease progression (page 7459, column 1).

Applicants disagree. For clarity, claim 190 has been amended to recite that the method of treatment prevents the progression of prostate cancer or delays the progression of prostate cancer. The amendment makes clear that the method is not drawn to preventing prostate cancer but instead further defines how the treatment is occurring. This amendment obviates the Office's arguments above related to preventing prostate cancer. Regarding preventing the progression or delaying the progression of prostate cancer, Morris shows that the claimed methods are effective. As discussed above, Morris demonstrates that unconjugated J591 antibody was effective in preventing the progression of prostate cancer. According to Morris, progressive disease could be

documented by rising prostate-specific antigen (PSA) (at page 7455, first col.), and one patient in the study showed a PSA decline of 50%, while three others showed PSA stabilization (page 7459, first col.). This is unequivocal evidence that J591 is effective in preventing the progression or delaying the progression of prostate cancer. Withdrawal of the enablement rejections of claim 190 is respectfully requested.

At least for the reasons presented above, withdrawal of all enablement rejections is respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 69-71, 77-80, 125, 126, 129, 130, 136-140, 144, 150, 152-154, 156-161, 164, 165, 171-173, 186, and 190 as allegedly being anticipated by U.S. Patent No. 6,962,981 ("Murphy"), as evidenced by Liu *et al.* (*Cancer Res.* 1998. 58:4055-60) ("Liu") and George *et al.* (*Circulation.* 1998. 97:900-906) ("George") (at page 32). According to the Examiner, "absent a showing of any difference, the antibodies and antigen binding fragments disclosed by Murphy et al., are deemed the same as the claimed antibodies and antigen binding fragments thereof." (at page 34). Applicants traverse. On October 28, 2002, Applicants mailed a 1.131 Declaration by Dr. Neil Bander with the response to the Office Action. The Declaration removed Murphy as prior art reference. PAIR shows receipt of "Affidavit(s) Rule 131 or 132 or Exhibits" on November 4, 2002. The Declaration can be found in PAIR under "Applicant Arguments/Remarks Made in an Amendment" of November 4, 2002. The Declaration obviates the present rejection.

The Examiner also rejected claims 69, 77-80, 125-127, 129, 130, 136, 137, 139-141, 147, 150-155, 159, 171-173, 186, and 190 as allegedly being anticipated by U.S. Patent No. 5,538,866 ("Israeli"), as evidenced by George and Liu (at page 35). The Office Action stated on pages 36:

[a]lthough Israeli et al. does not expressly teach [that] any of the disclosed polyclonal or monoclonal antibodies or antigen binding fragments thereof "compete" for binding to PSMA with monoclonal antibodies J591, 415, J533, and/or E99, *because the disclosed antibodies bind the extracellular domain of*

*PSMA* (see, e.g., Figure 20), there is a reasonable presumption that the antibodies bind the same or an overlapping epitope of *PSMA* as those recognized by one or more of monoclonal antibodies J591, J415, J533, and E99.

First, Applicants note that a rejection over Israeli has already been made and overcome during the prosecution of this application. See the Reply to the January 23, 2003 Office Action.

Regardless, Applicants address this rejection again below.

It appears that the Examiner is making an inherency argument, pointing out that while Israeli does not teach all features of the present claim, it inherently anticipates them. Applicants disagree. A reasonable presumption that Israeli's antibodies compete with the antibodies of the claimed methods is a mere possibility, not a necessary result. According to MPEP 2112. IV. and the Federal Circuit law, "[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient" (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). Further, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art" (MPEP 2112.IV, quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990), emphasis in original). Israeli discloses hypothetical antibodies directed toward three, specific peptides (col. 6, lines 48-52), but does not teach or suggest that these antibodies compete for binding to *PSMA* with the antibodies of the claimed methods. Examiner's reasonable presumption that Israeli's hypothetical antibodies compete with the present antibodies does not prove that such competition necessarily flows from Israeli. Just because the hypothetical antibodies are directed against specific peptides of *PSM* antigen does not necessarily mean that they would compete with the present antibodies.

In fact, the peptides disclosed by Israeli are not capable of generating antibodies that bind *PSMA*, period, forget bind to *PSMA* to compete for binding. Applicants submit herewith as Exhibit B, Holmes (2001) *Exp. Opin. Invest. Drugs* 10(3): 511-519 ("Holmes"), which shows that the antibodies produced according to the techniques disclosed in Israeli do not bind to *PSMA*. Holmes teaches that rabbits were immunized with KLH-conjugates with aa63-68,

aa132-137 or aa482-487 of PSMA. These correspond to SEQ ID 35, 36 and 37 as disclosed in Israeli. Holmes state that:

No binding to full length PSMA could be demonstrated with these antisera under conditions that gave saturating peptide activity. Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability. This observation may be a property of the antibodies to these protein regions, or perhaps can be overcome by the use of slightly longer eight amino acids ..." (page 513, first column, lines 6-14).

From Holmes, it is clear that antibodies generated to the peptide disclosed in Israeli do not bind to PSMA, and thus would not compete for binding to PSMA with the antibodies recited in the claims.

Israeli also discusses polyclonal and monoclonal antibodies that generally bind to PSM antigen, without reciting any further characteristics of such antibodies (col. 6, lines 48-52). These antibodies are even further removed from the present antibodies. In fact, these Israeli's antibodies can be at best described as a genus of antibodies that bind to PSMA, and as such they do not anticipate the species of antibodies of the claimed methods. According to MPEP 2112.IV, "a prior art reference that discloses a genus still does not inherently disclose all species within that broad category" (quoting *Metabolite Labs v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004)). Thus, Israeli's monoclonal and polyclonal antibodies directed against PSM antigen are a broad genus that cannot anticipate the present antibodies produced by specific recited hybridomas.

The Office Action also states at page 36-37:

[m]oreover, as evidenced by George et al. (cited *supra*), an antibody need not bind to the same epitope of an antigen as another antibody to measurably "compete" for binding to the antigen with the other antibody. Thus, at a high enough concentration, or under certain conditions, *any* antibody, including an antibody that binds to a different epitope of an antigen than the epitope recognized by another antibody that binds the antigen is expected to "compete" for binding to the antigen with the other antibody . . . [T]he antibodies disclosed by the prior art are polyclonal; polyclonal antibodies raised against PSMA bind a plurality of epitopes of PSMA, and are reasonably expected to comprise one or more species of antibody that bind to the same epitopes as monoclonal antibodies

J591, J415, J533, and/or E99 and thereby “compete” for binding to PSMA with one or more of the monoclonal antibodies (emphasis added).

Applicants disagree. First, as discussed in depth above, competition assays were well-known in the art at the time of filing the application. Skilled practitioners, such as George, knew how to carry out controlled experiments to avoid false positives and determine which results constitute competition at the time of filing the present application.

Second, as discussed above, polyclonal antibodies taught by Israeli are a broad genus that does not anticipate the specific antibodies of the claimed methods. The Office seems to acknowledge that Israeli's polyclonal antibodies are a genus, when it states that they “are reasonably expected to comprise one or more species of antibody that bind to the same epitopes” as the instant antibodies (see quote above). A reasonable expectation is a mere possibility (not a necessary characteristic) that the broadly described polyclonal antibodies would compete for binding with the antibodies of the claimed methods. Thus, Israeli's polyclonal antibodies do not anticipate the present antibodies.

Further, the Office stated that:

[w]hile Israeli et al. may not expressly teach [that] the antibody or antigen binding portion thereof binds “live” cells, Israeli et al. discloses, for example, [that] the antibodies are useful to detect the expression of PSMA in living animals (see, e.g., column 12, lines 61 and 62); but moreover it is readily understood and appreciated that the prostate cancer cells expressing PSMA to which the antibody binds, so as to ultimately kill those cells, are very much *alive*. (at page 37).

Applicants disagree. As discussed above, Israeli does not teach or suggest that its monoclonal antibodies directed toward three specific peptides compete with the antibodies of the claimed methods. It is a mere possibility, and not a necessary feature that Israeli's antibodies might compete with the present antibodies. In fact, as discussed above, antibodies produced with the disclosed peptides do not bind PSMA. Further, other monoclonal and polyclonal antibodies disclosed by Israeli are a broad genus that does not anticipate the present claims. Israeli states that its “antibodies are useful to detect the expression of mammalian PSM antigen in living animals, in humans, or in biological tissues or fluids isolated from animals or humans” (col. 12,

lines 61-63). This is a broad assertion, describing a genus of antibodies that do not anticipate the species of antibodies of the claimed methods.

In addition, the Examiner stated that:

[f]urthermore, although Israeli et al. does not expressly teach [that] any of the disclosed antibodies is internalized with PSMA, as evidenced by Liu et al., each of monoclonal antibodies J591, J415, J533, and E99 are internalized with PSMA by LNCaP cells (see entire document; e.g., page 4056, column 1). Accordingly there is a reasonable presumption that the antibodies disclosed by Israeli et al., which bind to the extracellular domain of PSMA, are internalized with the antigen, particularly since the disclosed antibodies are deemed to "compete" for binding to PSMA with monoclonal antibodies J591, J415, J533, and/or E99. (at pages 37-38)

As discussed *supra*, Applicants submit that Israeli discloses three antibodies directed against specific peptides but as discussed above these peptides do not give rise to antibodies that bind PSMA. Israeli also discusses a broad genus of antibodies that do not anticipate those of the claimed methods. Liu does not indicate that Israeli's antibodies possess all the features of the present claims. Thus, Israeli does not anticipate the present claims.

At least for the reasons presented above, Applicants respectfully request that all anticipation rejections be withdrawn.

#### Rejections under 35 U.S.C. § 103

The Examiner rejected claims 70, 71, 160, 161, 164, and 165 as allegedly being obvious over Israeli, as evidenced by George (at page 38). As discussed above, Israeli neither teaches nor suggests methods of treating, preventing, or delaying the development or progression of prostate cancer using antibodies or antigen-binding portions thereof that bind PSMA and compete for binding with the antibodies recited in the present claims. George (also discussed *supra*) does not remedy the deficiencies of Israeli. Therefore, Applicants respectfully request that all obviousness rejections be withdrawn.

### Double Patenting

The Examiner rejected claims 69, 70-74, 77-80, 125, 129, 130, 136-141, 147, 150-155, 159, 160, 161, 164-168, 171-173, 186, and 190 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 12 and 15-22 of U.S. Patent No. 6,136,311 (“311 patent”) in view of Israeli (at page 40). A terminal disclaimer is being filed herewith, thereby obviating this rejection.

The Examiner provisionally rejected claims 69-71, 77-80, 124-127, 129, 130, 136-155, 159-161, 164, 165, 171-173, 186, and 190 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 55-59 and 172-296 of co-pending Application No. 10/449,379 (at page 41).

Applicants note that this is a provisional rejection. This rejection will be addressed upon an indication of allowance in either of the pending applications.

The Examiner provisionally rejected claims 69-71, 77-80, 127, 129, 130, 136, 139, 140, 151, 159-161, and 190 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-61 of co-pending Application No. 11/219,563 (at page 42). Applicants note that claims 1-61 are no longer pending in the application no. 11/219,563. The published application (Pub. No. U.S. 2006/0088539) lists claims 1-61 as cancelled, and includes claims 64-116.

Applicants note that this is a provisional rejection. This rejection will be addressed upon an indication of allowance in either of the pending applications.

At least for the reasons presented above, withdrawal of all double patenting rejections is respectfully requested.

Conclusion

At least for the reasons presented above, Applicants respectfully submit that all claims are in condition for allowance, which action is expeditiously requested. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims. All amendments and withdrawals are made without prejudice and disclaimer and may be made for reasons not explicitly stated or for reasons in addition to ones stated.

Enclosed is a Petition for a Three-Month Extension of Time and a check for the required fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney's Docket Number 21052-003002.

Respectfully submitted,

Date: 7/19/07



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